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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/582,316	02/20/2007	Xin Lu	31265/5868A	1608

4743 7590 08/29/2008

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EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	PAPER NUMBER
1642	
MAIL DATE	DELIVERY MODE
08/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,316	LU ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,11-20 and 22-34* is/are pending in the application.

4a) Of the above claim(s) *11-17,19,20,22-28,30,31 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,18,29,32 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/8/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election of Group I, claims 1, 5, 18, 29, 32-33, SEQ ID NO:1 in the reply filed on 06/23/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Accordingly, Group I, claims 1, 5, 18, 29, 32-33, SEQ ID NO:1 are examined in the instant application.

Objection

1. Figure 3 is objected to, because it is not readable.

2. The specification is objected to, because the specification on page 25 recites figure 10 and figure 11. However, figures 10-11 are not found in the Drawings.

3. Claims 1, 5, 18, 29, 32-33 are objected to for the use of the language "represented by" in claim 1. It is not clear how the polypeptide is represented by the amino acid sequence of SEQ ID NO:3.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29, 32-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 29, 32-33 are indefinite, because it is not clear "sequence variant thereof" is the variant of SEQ ID NO:1 or of the p53 polypeptide. For the purpose of compact prosecution, the sequence variant thereof is interpreted as the sequence variant of SEQ ID NO:1.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5, 18, 29, 32-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, the specification must enable one skilled in the art to make and use the claimed invention without undue experimentation. The claims are evaluated for enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows: (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity

of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims. Such an analysis does not need to specifically enumerate (points 1-8) but only needs to have a select few of the factors present discussed in a rejection.

It is noted that the "sequence variant thereof" in claim 29 is interpreted as sequence variant of SEQ ID NO:1.

The specification discloses that figure 7 illustrates that p53 preferentially binds to the full length SEQ ID NO:1 (iASSP6C), while Bcl-2 preferentially binds to its variant iASPP (SEQ ID NO:3) described in WO200212325 (p.2, 25). The specification discloses that Figure 8 illustrates the activity of the full length iASPP6C in cells and that iASPP and p53 are involved in the activation of apoptotic genes but not cell cycle regulatory genes, and that it also interacts with p63 and p73 (p.25). The specification discloses that Figure 11 illustrates that the C-terminus of iASPP6C is required for the inhibition of p53 (p.25). The specification contemplates treating disease, such as cancer, using the claimed polypeptide (p.11).

Figure 11, however, is not found in the Drawings. Further, a review of figure 7 does not show that p53 preferentially binds to the full length SEQ ID NO:1 (iASSP6C), while Bcl-2 preferentially binds to iASPP (SEQ ID NO:3). It is not clear in figure 7 where the data is for SEQ ID NO:1. Further, although in figure 7, there are data for SEQ ID NO:3, the meaning of the data is unclear. Similarly, a review of Figure 8 does not show that SEQ ID NO: 1 inhibits the pro-apoptotic activity of p53, because it is not clear what is "Fold TA on PIG3 luc reporter", and how it is related to pro-apoptotic activity of p53.

1. Claims 1, 5, 18, 29, 32-33 are rejected under 35 U.S.C. 112, first paragraph for **lack of enablement of the claimed polypeptide, SEQ ID NO:1**, and a method for identifying agents that modulates the interaction between SEQ ID NO:1 and p53 polypeptide.

Without objective evidence, one cannot predict the claimed function of SEQ ID NO:1, such as its binding to p53 to inhibit the pro-apoptotic activity of p53, and its preferential binding of p53 to inhibit the pro-apoptotic activity of p53 when compared to SEQ ID NO:3.

A sequence similarity search shows that the sequence in WO200212325 is 37 % similar to SEQ ID NO:1 (MPSRCH search result, 2008, us-10-582-316.1.rag, result 7, pages 1-2). The function of SEQ ID NO:1 could not be predicted, based on sequence similarity with its variant iASPP, nor would it be expected to be the same as that of iASPP. Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1).

Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399 para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Further, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport proteins that included a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter "downregulated in adenoma". However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al. suggest that these results underscore the importance of confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph). In view of the above, one cannot predict the function of SEQ ID NO:1.

2. Further, even if the function of SEQ ID NO:1 were known, one would not know how to make the claimed **variant** such that it has the same function as SEQ ID NO:1. Similarly, one would not know how to make the variant of SEQ ID NO:3, such that it has the function of SEQ ID NO:3.

The specification, however, has not taught how to make the claimed variant of SEQ ID NO:1 or SEQ ID NO:3 that would be reasonably expected to have the function or properties of SEQ ID NO: 1 or SEQ ID NO:3, respectively. The specification does not disclose structure of the domain responsible for the function of SEQ ID NO:1 or SEQ ID NO:3. Although the specification asserts on page 25 that Fig 11 shows that the C-terminus of SEQ ID NO:1 (iASPP6C) is required for inhibition of p53, Figure 11 is not found in the Drawings. One would not know how to make the claimed variant, in view that protein chemistry is probably one of the most unpredictable areas of biotechnology. Bowie (Science, 1990, 257:1306-1310) teaches that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie further teaches that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col

2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein.

3. Claims 1, 18 are also rejected under 112, first paragraph, for lack of enablement of a **"pharmaceutical composition"** comprising SEQ ID NO:1.

A pharmaceutical composition encompasses in vivo use thereof, such as treating disease, such as cancer, as contemplated in the specification.

One cannot predict that the claimed polypeptide could be used for cancer treatment, because it is well known in the art that cancer immunotherapy is highly unpredictable. Mellman I, 2006, The Scientist, 20(1): 47-56, teaches that immunotherapy of cancer has yet to live up to expectations (p.47). Mellmann teaches that attempts at using cytokines to stimulate anticancer T cells, or deploying toxin-conjugated antibodies as magic bullets were never quite successful, and that therapeutic vaccines for cancer have proven similarly disappointing (p.47). White et al, 2001 (Ann Rev Med, 52: 125-145), teach that for a successful immunotherapy, besides the specificity

of the antigen, other following properties of the antigen should also be considered: The antigen should be present on all or near all of the malignant cells to allow effective targeting and to prevent a subpopulation of antigen-negative cells from proliferating. Further, antibodies have been developed against a broad spectrum of antigens, and whether the antigens shed, modulate or internalize influence the effectiveness of the administered antibody (p.126, second paragraph). Moreover, antigen internalization or downregulation can cause repeat dosing to be unsuccessful due to the disappearance of the antibody target (p.126, paragraph before last). Furthermore, cancer tolerance is a well known phenomenon. Bodey et al, 2000, Anticancer Res, 20: 2665-2676, teach that although general immune activation against the target antigens has been documented in most cases, reduction of tumor load has not been frequently observed in human patients (abstract, second column, p.2673). Bodey et al teach that the failure of cancer vaccine is due to natural selection of highly aggressive clones in the treated patient, said clones no longer express the cancer specific antigen (abstract, second column, p.2673). Bodey et al teach that these clones of tumor cells survive the immune system, through secretion of immunoinhibitory cytokines, downregulation of MHC, loss of costimulatory molecules, and induction of T cell anergy (p.2673, second column, last paragraph).

MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more

predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the above unpredictability, and in view of the complex nature of the invention, a lack of sufficient disclosure in the specification, and little is known in the art concerning the claimed invention, there would be an undue quantity of experimentation required for one of skill in the art to practice the claimed invention, that is commensurate in scope of the claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, LARRY HELMS can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
August 26, 2008

/Larry R. Helms/
Supervisory Patent Examiner, Art Unit 1643

MPSRCH search result, 2008, us-10-582-316.1.rag, result 7, pages 1-2

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RESULT 7
AAU78284
ID   AAU78284 standard; protein; 350 AA.
XX
AC   AAU78284;
XX
DT   18-JUN-2002  (first entry)
XX
DE   Human apoptosis stimulating protein inhibitor (I-APS).
XX
KW   Human; apoptosis stimulating protein; APS; cytostatic; gene therapy;
KW   inducer of apoptosis; breast cancer; I-ASP; ASP inhibitor; p53.
XX
OS   Homo sapiens.
XX
PN   WO200212325-A2.
XX
PD   14-FEB-2002.
XX
PF   06-AUG-2001; 2001WO-GB003524.
XX
PR   04-AUG-2000; 2000GB-00019018.
PR   08-DEC-2000; 2000GB-00029996.
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PR   26-MAY-2001; 2001GB-00012890.
XX
PA   (LUDW-) LUDWIG INST CANCER RES.
XX
PI   Lu X;
XX
DR   WPI; 2002-303979/34.
DR   N-PSDB; ABK12868.
XX
PT   Novel apoptosis stimulating protein and nucleic acid molecule encoding
PT   the protein for treating cancer, has ankyrin repeat, alpha-helical domain
PT   and SH3 domain capable of inducing apoptotic function of p53.
XX
PS   Claim 40; Fig 11; 130pp; English.
XX
CC   The present invention relates to a new apoptosis stimulating protein
CC   designated, ASP, comprising at least one ankyrin repeat, an alpha-helical
CC   domain and an SH3 domain, that is capable of inducing apoptotic function
CC   of p53. The molecules of the invention are useful for treating cancer in
CC   humans, by inducing apoptosis, or in manufacture of a medicament for the
CC   treatment of cancer. The protein or cells expressing the protein are
CC   useful for screening for agents (agonists, antagonist or a polypeptide)
CC   capable of modulating the activity of the ASP protein. The invention is
CC   also useful for preparing monoclonal antibodies which bind to the protein
CC   and can be used for manufacturing a medicament for the treatment of
CC   cancer, particularly breast cancer. The I-ASP (ASP inhibitor) polypeptide
CC   is useful for identifying agents with cell growth inhibitory activity and
CC   for inhibiting the activity of ASP-1, ASP-2 or I-ASP polypeptides or
CC   their binding partners. The present amino acid sequence represents the
CC   human apoptosis stimulating protein inhibitor (I-ASP) of the invention
CC   which inhibits the p53-stimulatory effect of ASP-2
XX
SQ   Sequence 350 AA;

  Query Match             37.8%;  Score 1671;  DB 5;  Length 350;
  Best Local Similarity   92.8%;  Pred. No. 2.8e-103;
  Matches  320;  Conservative    0;  Mismatches   25;  Indels    0;  Gaps    0;

Qy        483 PVARPLSPTRLQPALPPEAQSVPELEEVARVLAEIPRPLKRRGSMEQAPAVALPPTHKKQ 542
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          6 PVARPLSPTRLQPALPPEAQSVPELEEVARVLAEIPRPLKRRGSMEQAPAVALPPTHKKQ 65

Qy        543 YQQIISRLFHRHGGPGPGGPEPELSPITEGSEARAGPPAPAPPAPIPPPAPSQSSPPEQP 602
              ||||||||||||||||||      |          ||        |   ||||||||||||
Db         66 YQQIISRLFHRHGGPGPGGRSQSCPPSLRDLRPGQGPLLLPHQLPFHRPAPSQSSPPEQP 125

Qy        603 QSMEMRSVLRKAGSPRKARRARLNPLVLLLDAALTGELEVVQQAVKEMNDPSQPNEEGIT 662
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        126 QSMEMRSVLRKAGSPRKARRARLNPLVLLLDAALTGELEVVQQAVKEMNDPSQPNEEGIT 185

Qy        663 ALHNAICGANYSIVDFLITAGANVNSPDSHGWTPLHCAASCNDTVICMALVQHGAAIFAT 722
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        186 ALHNAICGANYSIVDFLITAGANVNSPDSHGWTPLHCAASCNDTVICMALVQHGAAIFAT 245

Qy        723 TLSDGATAFEKCDPYREGYADCATYLADVEQSMGLMNSGAVYALWDYSAEFGDELSFREG 782
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        246 TLSDGATAFEKCDPYREGYADCATYLADVEQSMGLMNSGAVYALWDYSAEFGDELSFREG 305

Qy        783 ESVTVLRRDGPEETDWWWAALHGQEGYVPRNYFGLFPRVKPQRSK 827
              |||||||||||||||||||||||||||||||||||||||||||||
Db        306 ESVTVLRRDGPEETDWWWAALHGQEGYVPRNYFGLFPRVKPQRSK 350
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